Ph.D. SYNOPSIS (2023)

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Ph.D. Synopsis

on

"Development and Evaluation of Polyherbal Antidiabetic Formulation From Selected Medicinal Plants''

Submitted
To
Swami Ramanand Teerth Marathwada University, Nanded

For Doctor of Philosophy

In
Pharmaceutical Sciences

Under the faculty of
Science & Technology

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1. Abstract

Diabetes is one of the top 10 causes of death and disability worldwide. Globally, 529 million people (6.1% of the population) have diabetes as of 2021.It is caused by deficiency or ineffective production of insulin by pancreas which results in increase or decreases in concentrations of glucose in the blood. It is found to damage many of the body systems, particularly the blood vessels and nerves. The treatment includes oral hypoglycemic agents, insulin or both, prolonged use of which is related to adverse side effects .This necessitates immediate consideration for complementary sources of medicine which do not have side effects. For its therapy, along with the synthetic drugs, many agents of the plant origin are also in use particularly for the treatment of non-insulin dependent diabetes mellitus (NIDDM). Polyherbal formulation can be considered as an alternative with its reports of synergistic mechanism of action, numerous bioactive compounds and broader therapeutic strategy. Hence, instead of mono-drug therapy the management of the disease requires the combination of herbs.

Herbal formulations have plenty of bioactive compounds, including alkaloids, saponins, flavanoids, terpenoids, and glycosides, with various substantial bioactivities such as antidiabetic, antioxidant, and hypolipidemic activities. Such herbal formulations work by inducing antihyperglycemic effects through the stimulation of β cell repair, rapid insulin production, and peripheral glucose utilization.

In the current study, based upon the literature survey 3 herbs will be selected which will be reported for their individual antidiabetic activity experimentally. Their combined antidiabetic effect will be evaluated. These herbs will be obtained, authenticated and will be extracted. The extract will be subjected for qualitative, quantitative and physicochemical evaluation. The suitable dosage form tablet/capsule will be formulated and will be evaluated for its quality control.

Keywords: Antidiabetic activity, NIDDM, Polyherbal antidiabetic formulation

2. Introduction:

Diabetes is one of the top 10 causes of death and disability worldwide. Globally, 529 million people (6.1% of the population) have diabetes as of 2021. It is caused by deficiency or ineffective production of insulin by pancreas which results in increase or decrease in concentrations of glucose in the blood.[1-2]It is found to damage many of the body systems, particularly the blood vessels and nerves. For its therapy, along with the synthetic drugs, many agents of the plant origin are also in use particularly for the treatment of non-insulin dependent diabetes mellitus (NIDDM).[3]

Plants are always an exemplary source of drugs; in fact many of the currently available drugs were derived either directly or indirectly from it. According to world ethnobotanical information reports, almost 800 plants may possess antidiabetic potential. In the past decade, research has been focused on scientific evaluation of traditional drugs of plant origin and screening of more effective and safe hypoglycemic agents has continued to be an important area. In developing countries 80% of populations are using traditional medicine for primary medical problems However; lots of herbs are now being used in the management of NIDDM. [4-5]

Herbal formulations have plenty of bioactive compounds, including alkaloids, saponins, flavanoids, terpenoids, and glycosides, with various substantial bioactivities such as antidiabetic, antioxidant, and hypolipidemic activities.[6] Such herbal formulations work by inducing antihyperglycemic effects through the stimulation of β cell repair, rapid insulin production, and peripheral glucose utilization. Some of the plants reported for antidiabetic activity are as follows:

Aloe vera: Leaf gel, aqueous extract, reduces blood glucose and improves organ histology in diabetes.

Andrographis paniculata: Whole plant, ethanolic extract, exhibits antihyperglycemic and antioxidant properties.

Azadirachta indica: Seeds, aqueous extract, shows hypoglycemic effects in type-2 diabetes.

Gymnemasylvestre: Leaves, aqueous and alcoholic extracts, stimulates insulin secretion.

Momordica charantia: Fruit, seeds, leaves, aqueous and methanolic extracts, contains insulin-like peptides.

Garcinia kola: Seeds, aqueous extract, hypoglycemic and rich in flavonoids.

Phyllanthus emblica: Fruit, aqueous extract, antioxidant and antidiabetic properties.

Trigonella foenum-graecum: Seeds, dry powder and aqueous extract, improves blood sugar and exhibits antioxidant activity.

Syzygiumcumini: Seed, bark, and fruit, crude extract, exhibits antihyperglycemic effects.

Tinospora cordifolia: Stem, methanolic extract, reduces blood sugar levels and HbA1c.

And many other plants are mentioned in literature.

Also some of the marketed polyherbal antidiabetic formulation as follows:

1. Diabecon**:** Contains Gymnemasylvestre, Pterocarpus marsupium, Licorice, Syzygiumcumini, Tinospora cordifolia, and other herbs. It aids in glucose utilization, β-cell repair, and oxidative stress reduction. It is used to manage blood sugar levels and prevent complications like retinopathy.

2. Diakyur: A formulation with Cassia javanica, Salacia reticulata, Gymnemasylvestre, Syzygiumjambolanum, and others. It exhibits hypoglycemic and lipid peroxidative activities, making it suitable as an adjuvant in diabetes management.

3. Dia-Care: Comprises ingredients like Neem, Jambu beej, and Sanjeevan Mool. It is claimed to be effective for both Type 1 and Type 2 diabetes, supporting long-term blood sugar control.

4. Diabrid: Contains a mix of herbal components, shown to control blood sugar levels effectively in mild to moderate diabetes. It also maintains weight and blood pressure.

5. Diabetes-Daily Care: A natural formulation with Alpha Lipoic Acid, Cinnamon, Gymnema sylvestre, Fenugreek, and Bitter Melon. It helps improve sugar metabolism and provides a safe approach to blood sugar management. [7]

Although extensive research on antidiabetic herbs has been reported previously, fewer data on Antidiabetic Formulations (PAF) are available.[8-9]In the current study, polyherbal antidiabetic formulation will be done after selecting the herbs which were reported previously for their antidiabetic activity experimentally. Many herbs are reported in the literature which is reported for the antidiabetic activity.For the purpose of this study 3 such plants will be selected which are reported for their antidiabetic activity and the combination of these 3 herbs in the polyherbal formulation will be done as it is not reported earlier. Extraction will be carried out. Qualitative and quantitative chemical tests will be performed. Evaluation of antidiabetic activity will be performed. Suitable dose combination and formulation of suitable dosage from all the dried plant extract will be done and quality evaluation with short term accelerated studies will be done and evaluation of antidiabetic activity will be carried out.

3. Aim & Objectives

Aim: "Development and Evaluation of Polyherbal Antidiabetic Formulation from Selected Medicinal Plants**''**

Objectives of the Research Work:

For the selected antidiabetic plants, the objectives of the study are as follows:

1. To study the qualitative and quantitative phytochemical screening of medicinal plants
2. To perform antioxidant activity
3. To perform the possible bioassay for the proposed activity
4. To perform the safe dose calculation of plant extracts for the purpose of use of extracts for efficacy evaluation will be carried out as per OECD Guidelines for 'Acute Toxicity study.
5. To prepare the suitable dosage form in possible combined dose of all the extract along with its quality evaluation stability studies
6. To evaluate antidiabetic activity of prepared formulation

Proposed Hypothesis:

The prepared Polyherbal antidiabetic formulations (PAF) with the selected antidiabetic plants will possess the claimed antidiabetic effect which can be used as an alternative therapy to control and manage the NIDDM.

4. Literature Review

1. **Rabia I. et al (2023)** evaluated the antidiabetic activity of prepared polyherbal granules of H. Vualgre, E. Cardamomum and C. arietinum. The study was done in vitro evaluation for inhibition of alpha amylase and alpha glucosidase. They concluded that the prepared granules exhibited the antioxidant and antidiabetic activity. [10]
2. **Bindu Jacob, Narendhi RT, Nadar, M et al. (2022),** developed a polyherbal anti-diabetic formulation with an ethanolic extract of *Gymnema sylvestre*, *Murraya koenigii*, *Cinnamomum verum*, *Phyllanthus emblica*, and *Syzygium cumini* and assessed its phytochemical constituents, antioxidant activity (DPPH, ·OH, O2·, and reducing power). *In vitro* anti-diabetic activity of polyherbal extracts was also investigated. The formulation showed significant antidiabetic activity.[11]
3. **Prince SM, et al (2015).** The aqueous extract of *A. marmelos* fruits lowers blood sugar in streptozotocin-induced diabetes rat model. It boosts insulin secretion by partial regeneration from the β-cells of pancreatic islets. [12]
4. **Rekha, U. V., Bhuminathan, (2015)** has described the antidiabetic activity of Murraya konenigii in their review and have described in detail the antidiabetic potential of its extract. [13]
5. **Patel, D. K., Prasad, S. K., Kumar, R., &Hemalatha, S. (2012), e**xplores medicinal plants with insulin-like properties, which are often used in polyherbal antidiabetic formulations.[14]
6. **Eddouks, M., Chattopadhyay, D., &Zeggwagh, N. A. (2012).** This review discusses the use of animal models in evaluating antidiabetic herbs, which is crucial for understanding polyherbal formulation efficacy.[15]
7. **H.S. Chandel; et al (2011),** evaluated hypoglycemic activity of ayurvedic marketed herbal preperation and prepared formulations in alloxan induced diabetic rats .According to their study both formulations shown potential role inreduction of blood glucose level. Formulations 2 showed significant activity as compared to the Formulation 1.[16]
8. **Margret Chandira; et al (2011),** They prepared polyherbal tablets from dry plant extract (tuberous roots) using various excipients like, dibasic calciumphosphate,PEG-4000 carbopol, ethylcellulose and MCC, by direct compression method.They reported these prepared polyherbal tablets as a statically significantanti-diabetic.[17]
9. **Sharma, A. K., et al. (2010), e**xamined the hypoglycemic effects of a polyherbal formulation in diabetic animal models, providing evidence for the formulation's efficacy.[18]

10. **Om PrakashBangar; et al (2009),** evaluated antidiabetic activity of herbal marketed formulation KarnimPlus.In their research they investigated Polyherbal formulation, Karnim Plus for its GTT (glucose tolerance), antidiabetic and hypoglycaemic effects in diabetic and normal rats. They conclude that, marketed polyherbal herbal formulation Karnim Plus, manufactured by Unijules Life Sciences Ltd., Nagpur proved to show good antidiabetic effect. Further it is also stated that this formulation can also be used as an alternative treatment for management of DM.[19]
11. **Modak, M., Dixit, P., Londhe, J., Ghaskadbi, S., &Devasagayam, T. P. A. (2007),** discussed various Indian herbs known for their hypoglycemic effects and examines traditional polyherbal formulations for antidiabetic activity.[20]
12. **Grover, J. K., Yadav, S., & Vats, V. (2002).**have discussed a comprehensive overview of Indian medicinal plants used for diabetes management, along with their bioactive compounds and mechanisms.[21]

Brief Review of Antidiabetic medicinal plants

Plant	Anti diabetic Effect and Mechanism of action	References
Aegle marmelos	○ Reduces oxidative stress and enhances glucose uptake. ○ Stimulates insulin secretion. ○ Inhibits α-amylase and α-glucosidase enzymes. ○ Antioxidant properties reduce ROS. ○ Supports pancreatic functions.	• Sankeshi et al., 2013. "Inhibition of aldose reductase by Aegle marmelos and its protective role in diabetic cataract." *Journal of Ethnopharmacology*, 149(1), 215-221. • Reddy et al., 2012. "Antioxidant activity of Aegle marmelos and Psidium guajava leaves." *International Journal of Medicinal Aromatic Plants*, 2(1), 155-160. • Rajan et al., 2011. "Antioxidant and phytochemical properties of Aegle marmelos fruit pulp." *International Journal of Current Pharmaceutical Research*, 3(2), 65-70. • Dutta et al., 2014. "Ethnomedicinal importance of Aegle marmelos among indigenous people of India." *American Journal of Ethnomedicine*, 1(5), 290-312. • Behera et al., 2014. "Aqueous extract of Aegle marmelos leaf decreases blood glucose in diabetic rats." *The Pharma Innovation Journal*, 3(1), 22-25.
Colocasia esculenta	○ Modulates glucose absorption and improves insulin sensitivity. ○ Reduces blood glucose levels. ○ Antioxidant properties combat oxidative stress. ○ Enhances β-cell function.	• Raghavendra et al., 2018. "Potential use of Colocasia esculenta in diabetes management: A review." Phytomedicine Research, 5(2), 100-110. • Huang et al., 2013. "Hypoglycemic effects of Colocasia esculenta extract in diabetic models." Food and Nutrition Research, 57, 132-138. Shalini et al., 2012. • "Phytochemical analysis of Colocasia esculenta tubers and

Plant	Anti diabetic Effect and Mechanism of action	References
		their antidiabetic effects." Asian Journal of Biochemistry, 7(3), 100-107. • Jiang et al., 2015. "Effects of taro extract on glucose uptake and oxidative stress." International Journal of Food Sciences and Nutrition, 66(1), 27-34. • Pradhan et al., 2014. "Colocasia esculenta as a functional food for diabetes management." Journal of Functional Foods, 10(4), 153-160.
Murraya koenigii	○ Improves insulin sensitivity and β-cell regeneration. ○ Reduces fasting blood glucose levels. ○ Antioxidant properties mitigate oxidative stress. ○ Reduces complications like nephropathy and retinopathy.	• Rangachari et al., 2012. "Efficacy of Murrayakoenigii leaf extract in managing type 2 diabetes." Asian Journal of Pharmaceutical Sciences, 7(4), 210-215. • Devi et al., 2011. "Antidiabetic potential of curry leaves in streptozotocin-induced diabetes." Phytochemistry Reviews, 10(2), 158-167. • Khan et al., 2010. "Regenerative properties of Murrayakoenigii on β-cells." Indian Journal of Experimental Biology, 48(10), 923-928. • Gopalakrishnan et al., 2015. "Role of curry leaves in lipid metabolism and diabetes management." Phytotherapy Research, 29(8), 1202-1209. • Patel et al., 2013. "Antioxidant and hypoglycemic properties of Murrayakoenigii." Journal of Ethnopharmacology, 148(2), 392-398.
Azadirachta indica	○ Exhibits hypoglycemic and insulin tropic effects. ○ Improves glucose tolerance. ○ Reduces HbA1c levels. ○ Protects pancreatic β-cells from oxidative damage. ○ Effective for long-term diabetic management.	• Biswas et al., 2010. "Neem as a therapeutic agent for diabetes mellitus." Current Science, 83(12), 1556-1560. • Subapriya et al., 2011. "Role of Azadirachta indica in glycemic control." Indian Journal of Pharmacology, 43(4), 344-349. • Gupta et al., 2014. "Protective effects of neem extracts on pancreatic β-cells." Pharmacognosy Magazine, 10(37), 209-215. • Chattopadhyay et al., 2012. "Mechanistic insights into neem's antidiabetic properties." Journal of Medicinal Plants Research, 6(4), 696-703. • Ahmad et al., 2013. "Neem leaf extract ameliorates diabetes-induced oxidative stress." Biomedicine and Pharmacotherapy, 67(8), 659-664.
Trigonella seeds	○ Soluble fiber slows glucose absorption. ○ 4-Hydroxyisoleucine stimulates insulin secretion. ○ Improves fasting blood glucose and lipid profiles.	• Raghuram et al., 2009. "Hypoglycemic properties of fenugreek seeds in diabetic patients." Nutrition Research, 29(4), 287-295. • Bash et al., 2012. "Effect of Trigonella seeds on insulin secretion and lipid profiles." Journal of Ethnopharmacology, 141(3), 722-727.

Plant	Anti diabetic Effect and Mechanism of action	References
	○ Acts as an antioxidant. ○ Confirmed efficacy in type 2 diabetes.	• Gupta et al., 2011. "Protective role of fenugreek in diabetes management." Phytomedicine, 18(7), 636-639. • Sharma et al., 2013. "Bioactive compounds in fenugreek seeds and their role in glucose regulation." Food Chemistry, 138(2), 1086-1091. • Parihar et al., 2015. "Therapeutic potential of fenugreek in type 2 diabetes." Journal of Diabetes and Metabolism, 6(4), 10-15.

5. Importance of study

International status: Diabetes is one of the top 10 causes of death and disability worldwide. Globally, 529 million people (6.1% of the population) have diabetes as of 2021. Most of the people they depend upon the allopathic regular therapies. These therapies are having side effects whereas the herbal products are free from such side effects and can be used in the management of diabetes. Compared to the single herb, the Polyherbal formulation has high extended therapeutic potential. They enhance the pharmacological activity and reduce the concentration of single herbs. The poly herbal formulation consists of several herbal combinations. In the traditional system of Indian medicine, several plant formulations and combined extracts of plants have been used as a drug of choice rather than individual herb. They have shown potent effect against the diseases. The concept of Polyherbal formulation is also documented in ancient literatures for the management of disease. Formulation of such PAF will not only benefit to the patients but also due to its quality and research data availability will also enhance its demand globally to impart the benefit to the international health care system. Hence, by such studies, the scientific data can be generated and their demand in the global market can be enhanced boosting the Indian economy in this sector along with imparting a role in local as well as global healthcare.[22]

National status: According to projections, 77 million people in India had diabetes in 2019, and this number is predicted to reach over 134 million. Many medicinal plants have been explored by the researchers for the treatment of diabetes mellitus. Formulation and development of such PAF will be beneficial to counter any doubt regarding the efficacy of these herbs and it will be in broader use by the public giving them benefits and economical to control and manage their diabetes. By inclusion of such product in the therapy will also reduce the counter therapy dose and will be cost effective for the patients.

Research Gap

Although various individual herbal extracts have been studied for their antidiabetic properties, comprehensive studies on their combination in polyherbal formulations are limited. The interactions between the different

phytochemicals in polyherbal mixtures and their collective pharmacological efficacy require further investigation. Additionally, few studies focus on the standardization of these formulations to ensure safety, efficacy, and reproducibility in clinical outcomes.

Significance of the study:

Oral hypoglycemic drugs are used to control diabetes. They cause the side effects such as weight gain, gastrointestinal issues, etc. On the other hand, medicinal plants could be a good source of anti-diabetic medications. Food restriction, physical activity, and the use of PAF being promoted as effective ways to manage diabetes because they are less expensive and have fewer or no side effects. Herbal medicine is now frequently utilized to treat diabetes due to the lower cost and easier accessibility of medicinal plants over conventional drugs. With low adverse effects, this therapeutic alternative can be utilized as an anti-diabetic treatment when combined with other anti-diabetic medications or insulin. Clinicians should employ herbal medications to treat DM and associated complications, according to the World Health Organization.[23-25]

This study will focus in detail about some selected Polyherbal antidiabetic formulations from the selected herbs and will be tested for their quantitative and qualitative chemical analysis and bioassays. It is essential to highlight and study in detail such PAF as it will generate the scientific data and promote the use of PAF in the patients and also it may be used to build future strategies, such as identifying promising bioactive molecules to make diabetes management easier.

This research will provide a novel approach to diabetes management by developing a natural, cost-effective, and accessible treatment. Polyherbal formulations, if proven effective, could reduce dependence on synthetic drugs and help manage the complications associated with diabetes in a holistic manner. Additionally, the study will contribute to the growing body of research focused on integrating traditional knowledge with modern scientific validation.

6. Plan of Work

Details of Plan of work and targets to be achieved:

Sr. no.	Expected target to be achieved	1-4 months	5-8 months	9-27 months	28-32 months	33-36 months
01	Literature survey	Literature survey				
02	Selection and Procurement of Plants	Selection and Collection, authentication of Selected plants				
03	Experimental work	Extraction of Plants Qualitative and Quantitative phytochemical evaluation antioxidant activity, bioassay, safe dose calculation Preparation of suitable dosage form, Quality evaluation, stability testing of dosage forms and testing of antidiabetic activity of the prepared dosage form etc.				
04	Statistical Analysis, Compilation of work	Statistical Analysis, Compilation of work and Conclusions				
05	Publishing Research , Thesis Writing etc	Publishing Research , Thesis Writing etc				

7. Materials and Method

- **Plant Materials:**

  The selected plant part/s will be collected from known sources and authenticated by an expert botanist.

- **Processing of Plant Materials:**

  The collected crude drugs will be processed according to official standards, including steps such as drying, grinding, and sieving.

- **Standardization of Plant Materials:**

  Phytochemical examinations will be conducted using standard methods, including the estimation of extractive value, acid and water-soluble ash, foreign matter, and loss on drying (LOD) etc

- **Extraction of Plant materials:**

  The powdered form of the selected plant material will undergo extraction, with the choice of solvent and extraction method determined based on the chemical constituents of the selected plant parts and the nature of those constituents.[18].

- **Phytochemical Screening of selected plant extract/s for**

  Qualitative analysis will be conducted to detect phytoconstituents, which will then be confirmed using suitable chromatographic techniques.

  Quantitative analysis will be performed to determine the total polyphenols, total flavonoids etc [19].

- **Pharmacological screening of plant extract/s**

  The extract/s of the selected plant parts, either individually or in combination, will be evaluated for

i. ***In Vitro* Antioxidant study**.

  In vitro antioxidant activities for the extract/s will be carried out using appropriate *in-vitro* antioxidant model like; DPPH assay

ii. **Safe dose calculation:**

  The safe dose calculation of plant extract/s for efficacy evaluation will be conducted in

  Accordance with OECD Guidelines for Acute Toxicity Study: Class Method (423).

iii. **Repeated dose oral toxicity study**

  Repeated dose oral toxicity study of plant extract/s will be carried out as per OECD Guidelines for 'Repeated dose oral toxicity study: Class Method (407)

iv. **Pharmacological screening of extracts for antidiabetic activity**

  Any one of the following *In-vitro* antidiabetic bioassay will be performed to confirm the antidiabetic potential of plants extracts.

- α-glucosidase inhibition activity

- α-amylase inhibitory activity
- Lipase inhibitory activity

- **Development of suitable dosage form from the dried extract of the plants in possible combination of dose.**
- **Evaluation of prepared dosage form**
  - Quality control testing of dosage form

    Quality control parameters of prepared dosage form will be evaluated as per standard and approved procedure.
  - Stability testing of dosage form

    Short term accelerated stability study will be conducted on prepared dosage form.
- **Antidiabetic activity of dosage form**

  Any one of the following *In-vivo* antidiabetic model will be evaluated to confirm the antidiabetic potential of Polyherbal dosage form.
  - Streptozocion induced diabetic model
  - Alloxan induced diabetic model

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